(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
15 November 2001 (15.11.2001)

PCT

(10) Internati nal Publication Number
WO 01/85801 A1

(51) International Patent Classification[7]: C08B 37/08, C08J 3/24, C08K 5/12

(21) International Application Number: PCT/EP01/05031

(22) International Filing Date: 3 May 2001 (03.05.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
MI2000A001030 10 May 2000 (10.05.2000) IT

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/85801 A1

(54) Title: CROSS-LINKED POLYMERS USEFUL FOR THE PHARMACEUTICAL, MEDICAL AND COSMETIC USES

(57) Abstract: A process for the preparation of cross-linked polymers by reacting macromolecules containing primary or secondary amino groups with suitably activated dicarboxylic acids which comprises: a) activating the dicarboxylic acid carboxy groups in anhydrous aprotic solvent; b) reacting the polyamino polymer, optionally previously subjected to partial "quenching" reaction of the amino groups; c) optionally reacting the resulting product from step b) with "quenching" agents of the residual amino groups.

CROSS-LINKED POLYMERS USEFUL FOR THE PHARMACEUTICAL, MEDICAL AND COSMETIC USES

Field of the invention

The present invention relates to a process for cross-linking polymers containing primary or secondary amino groups, (polyamino or cationic polymers) with suitably selected, activated dicarboxylic acids. Said controlled, reproducible process provides products with cross-linking degree up to 100%. The process includes the possible "quenching" of the residual amino groups by sulphation, hemisuccinylation, or reaction with dialkylamides or acrylic acid alkyl esters, or with suitably activated, pharmacologically active carboxy derivatives. A further object of the invention are the resulting products and the use thereof in the pharmaceutical (pro-drugs), medical (surgical and medical devices) and dermocosmetic fields.

A further object of the invention are the complexes of said cross-linked polymers with metal cations, for example: copper, zinc, iron, and the biomedical applications thereof.

Technological background

In recent years, the use of macromolecules in the pharmaceutical/medical field and, more recently, in the dermatological-cosmetic field, is increased. Exhaustive descriptions of the type of macromolecules used and of their applications can be found in:

1) "Comprehensive Medicinal Chemistry" - C. Hansch et Al. Editors- Pergamon Press, Oxford, 1990 - Vol. 1-6.

2) "Handbook of Pharmaceutical Excipients"- A. Wade & P.J. Wellers Editors- The Pharmaceutical Press - 1994.

3) "High Performance Biomaterials"- M. Szycher Editor- Technomic

Publ., 1991.

4) "Polymeric Drugs and Drug Delivery Systems" - R.L. Dunn & R.M. Ottenbrite Editors - ACS Symposium Series 469 - American Chemical Society, WA, DC, 1991.

5) "Biorelated Polymers and Gels; controlled-release and Applications in Biomedical Engineering" - Teren Okano Editor- Academic Press, 1998.

6) "Transport Processes in Pharmaceutical Systems" - G.L. Amidon, I. Lee, E. M. Topp Editors- Marcel Dekker Inc., 2000.

7) "Cosmetic Dermatology" - R. Baran & H.I. Maibach Editors- Martin Dunitz,1994.

The used macromolecules belong to different chemical families and may be either synthetic, natural or semi-synthetic. Said macromolecules can have linear or variously branched structure; they can optionally have functional groups in the side chains; composition and structure being equal, they can have different molecular weights, different molecular weight dispersion and the like.

Examples of linear synthetic macromolecules comprise: polyvinylpyrrolidone; polyoxyethylene alkyl ethers; polyvinyl alcohols, etc.

Examples of natural linear macromolecules include: cellulose, native hyaluronic acid (HY), chitosan, etc.

Examples of natural-semi-synthetic macromolecules include carboxyalkylcelluloses, widely used in the food and personal care industries.

Such macromolecules have been used for a long time for the preparation of solid formulations (as thickening agents, lubricants, disgregrants, film-formers for gastric resistance, controlled release agents, etc.); ointments or gels for the dermatological, cosmetic, ophthalmic uses

and the like. More recently, some of them are being used in injectable formulations (cutaneous fillers: hyaluronic acids, collagens etc.), others in the preparation of sponges, films, different devices such as surgical/medical devices (artificial skins, tissular antiadhesives, vascular prostheses, contact lenses, etc). An applicative field in full development is that of polymeric or oligomeric prodrugs (for a recent review, see: P. Ferruti and E. Ranucci, "Polymeric Drugs and Drug Delivery Systems" - Teren Okano Editor, ACS, 1991, pages 539-572), in order to improve a given active principle, both in terms of bioavailability (absolute and/or in time) and safety (avoiding plasmatic and/or tissular peaks potentially inducing undesired side effects). For this purpose, polymers or oligomers characterized by having, either in the primary chain or in the side ones, functional groups such as alcohol, amino, carboxylic, isocyanic groups, which are suitably bound with the active principles (ap) through esterification, amidation etc. The active principle is released by direct cleavage of the ap-macromolecule bond, optionally upon degradation of the macromolecule by the enzymatic systems of the body.

The application versatility of the macromolecules in the above mentioned fields can be increased by suitable structural changes, one of the most important being intermolecular cross-linking, which can be carried out on synthetic, semi-synthetic or natural polymers by means of suitable bi- or poly-functional molecules. Said process provides tridimensional (cross-linked) structures, which markedly differ in their chemical, physical, rheological, biological and processability characteristics from the starting macromolecules. Furthermore, the same macromolecule, after cross-linking, can have different final characteristics, depending on: type of cross-linking agent used; cross-linking degree (i.e. percentage of intermolecular bridges introduced with respect to the maximum degree possible); type of

macromolecule-cross-linking agent bond.

Examples of cross-linked polymers include: polyacrylates, carbomers, polyvinyl acetates, polymethylmethacrylates, hyaluronic acids, polycarboxylated polysaccharides (e.g. alginic acid), carboxyalkyl-polysaccharides (e.g. carboxymethyl starch, carboxyethyl-cellulose), celluloses, dextrans, etc.

Examples of used cross-linking agents include: bivalent inorganic ions (Ca, Ba); di- or polyfunctional epoxides; poly-alcohols; divinyl sulfone; dialdehydes; polycarboxylic acids (with formation of esters), etc.

Examples of patents concerning the cross-linking of the above mentioned polymers for biomedical purposes are the following:

US 465055 (alginic and hyaluronic acids, direct cross-linking); W091/09119 (alginic acid with barium ions); EP 0,190,215 (carboxymethyl-starch, dextran, cellulose with di- and polyfunctional epoxides); US 4,716,224, 4,772,419, 4,716,154 (various polymers with polyfunctional epoxides); US 4,957,744 (various polyalcohols); US 4,582,865, 4,605,691, 4,636,524 (various hyaluronic acids and divinyl sulfone); US 4,713,448, 4,582,865 (hyaluronic acids and dialdehydes); US 5,356,833 (hyaluronic acids carboxamides); EP-A-718,312 (hyaluronic acid and polycarboxylic acids); EP-A-566,118A7 (carboxylated polysaccharides and various cross-linking agents, inter alia polyamines).

The cross-linked compounds claimed by said patents have different uses, for example for the preparation of super-adsorbing gels for children, biohybrid organs with incorporation of cells, controlled-release formulations of active principles and dermocosmetics.

For all the bio-pharmaceutical considered applications, particularly for the preparation of invasive medical devices or of those which are in direct contact with blood or vascularized tissues, as well as for controlled-

release formulations, both macromolecules mentioned above and cross-linked derivatives should meet a number of technical and regulatory requirements.

The technical requirements include:

1) Biocompatibility of both the parent macromolecule(s) and the cross-link ap-macromolecule bond.

2) Modulable resistance to enzymatic systems, which can be: tissular (e.g. for articles such as artificial skins, surgical tissular antiadhesives, devices for the controlled release of the active principle); plasmatic (for controlled-release formulations); gastrointestinal (for oral formulations, such as gastroresistant tablets/capsules; enteral controlled-release forms, and the like). The enzymatic response should make the macromolecular component (optionally cross-linked) somewhat biodegradable so as to be readsorbed/excreted by the body without inducing side effects, and to provide the release of the active principle. In some cases, gradual enzymatic degradation, for instance for the controlled release of an active principle, may be desirable. A high resistance may be desirable in other cases, to maintain the device unchanged in time, particularly when the macromolecular component is present in formulations/articles that should last for long times, e.g. substitutes of the synovial liquid or cardiovascular prostheses (or their coatings) must have high resistance; on the other hand, tissular antiadhesive films or gels for different kinds of surgery, sponges for tissular engineering (bio- organs, such as pancreas, liver, artificial skins, cutaneous fillers for aesthetic surgery) require shorter degradation times in the body.

3) Resistance to wear in case the article has to be used for long times, particularly in case of cardiovascular devices or their biocompatible coatings.

4) Moldability into shapes suitable for different applications (gels, films, tubes, sponges, lenses, prosthesis coatings, etc.).

5) Possibility for the article to be sterilized chemically or physically without changing its macromolecular structure or characteristics.

According to the regulatory requisites in the pharmaceutical/medical field, the composition (and therefore the characteristics) of the different production batches of a given medicament or therapeutical device (independently on its therapeutical purpose) must be kept constant within very narrow limits. This therefore implies that the basic macromolecular components or their cross-linked derivatives have a very low composition variability (in terms of molecular weight or cross-linking degree) and that production methods are standardized.

In addition to the dispersion of molecular weights of the used linear polymers, the cross-linking process may be a further dishomogeneity factor. This may be a serious drawback in terms of field of use and applicative purposes of the final product.

Detailed disclosure of the invention

The present invention relates to a process for the preparation of cross-linked polymers by reacting macromolecules containing primary or secondary amino groups with suitably activated dicarboxylic acids; said controlled, reproducible process, provides all of the cross-linking degrees ranging from almost zero to 100% (with respect to the starting amino groups present). The presence of free amino groups makes the polycationic macromolecules intrinsically cytotoxicity, therefore part of the process of the invention - except when the cross-linking degree is 100% - is the "quenching" reaction of all the residual free amino groups of the polymer (i.e. those not cross-linked) by means of: sulphation agents (formation of N-sulfate residues); succinic anhydride (formation of N-hemisuccinic

residues); acrylic acid N',N'-dialkylamides or alkyl esters (Michael reaction with formation of N,N-diethyl-carboxy-N',N-'dialkylamides or N,N-diethyl-carboxy-alkylesters); carboxy derivatives, having pharmacological activity, suitably chemically activated. Alternatively, the process can include first the reaction for the partial "quenching" of the amino groups and then the reaction with the activated dicarboxylic cross-linking agent.

In particular, the process of the invention comprises the following steps:

a) activation of the cross-linking agent carboxy groups, in anhydrous aprotic solvent;

b) reaction with the polyamino polymer, to form amido bonds and cross-linking intermolecular bridges;

c) exhaustive reaction of the product from step b) with the above cited "quenching" agents of the residual amino groups (except when the cross-linking degree, obtained in b), is 100%).

Steps b) and c) of the process can be reversed (process a-c-b), preferably in case of "quenching" with pharmacologically active carboxy derivatives (formation of pro-drugs on cross-linked matrix). The "direct" process (a-b-c) is preferred when the final cross-linked product is designed as a pharmacologically inactive base (or as a moisturizer) for articles such as medical/surgical or dermocosmetic devices.

The cross-linked products obtainable by the process of the invention may, if desired, be complexed with metal ions such as copper, zinc, iron ions.

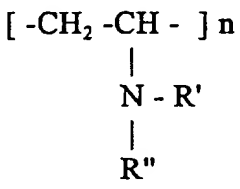
The polycationic macromolecules (containing primary or secondary amino groups) which may be used according to the invention may be of natural, semi-synthetic or completely synthetic origin. Examples of said macromolecules are:

Natural/semi-synthetic macromolecules

- hyaluronic acids (of bacterial or tissular origin) with different deacetylation degrees;
- collagens with different molecular weights;
- elastins with different hydrolysis degrees;
- chitosans with different molecular weights.

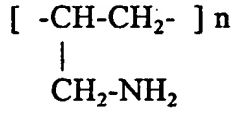
Synthetic macromolecules (commercially available or obtainable according to disclosed procedures):

- polylysines with different polycondensation degrees with acetylated or anyway protected N-terminus;
- poly(vinylamines) of general formula:

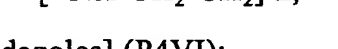


wherein R'= R"= H or R'= alkyl (linear or branched C_1-C_{12}) and R"= H;

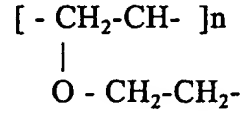
- poly (acrylamines), or poly (allylamines), of general formula:



- poly(iminoethylene) [or poly(ethyleneimines)] of general formula:



- poly [4, (5)- vinyl-imidazoles] (P4VI);
- poly [aminoethylmethacrylates];
- poly [β-aminoethyl] vinyl ethers of general formula:



Examples of suitable dicarboxylic cross-linkers which - after

activation with chloromethylpyridinium iodide (CMPJ) or other carboxy activators under conditions well-known to those skilled in the peptide synthesis - are capable of reacting with the cation polymer amino groups, inducing intermolecular cross-linking, comprise:

i) dicarboxylic acids of general formula:

$$HOOC - (X)_n - COOH$$
$$|$$
$$Y$$

wherein:

n is an integer of 2 to 18;

X is an alkylene chain, linear or branched, saturated or unsaturated, comprising 1 to 10 carbon atoms, optionally containing nitrogen or oxygen heteroatoms, for example amino acidic residues;

Y is an alkylene chain, linear or branched, saturated or unsaturated, comprising 1 to 10 carbon atoms, preferably 1 to 6 atoms, optionally containing, also in the side chains, groups of formula: -NRR' (wherein: R and R' = alkyl or acyl groups); -OR" (wherein: R"= H, alkyl or aryl and/or acyl groups); -COOR'" (wherein R'" = C_1-C_{10} alkyl groups, optionally branched or containing aromatic cycles or heterocycles);

ii) dicarboxylic amino acids, such as aspartic or glutamic acids, or the bi-condensed derivatives thereof, such as carboxy terminal monoesters;

iii) di- or poly-peptides deriving from the condensation of at least one acidic amino acid and neutral or basic amino acids;

iv) α- o β- malic acids or polymers thereof with low M.W.

The above mentioned cross-linking agents, in the form of tetrabutylammonium salts, are subjected to activation reaction with chloromethylpyridine iodide (CMPJ) in suitable anhydrous solvents, under nitrogen and at low temperatures. The activated product is then reacted with the selected cationic polymer.

The "quenching" reactions of the residual amino groups can then be carried out with known methods: SO_3-pyridine (in DMF and at 0°C); succinic anhydride (in aqueous phase and under vigorous stirring, keeping pH of 7.5 to 8.5 by means of sodium hydroxide); with acrylic acid N',N'-dialkylamides or alkyl esters, by direct reaction in aqueous or alcoholic or mixed medium, under strong stirring and nitrogen, keeping the temperature at about 15-25°C. The reaction can also be carried out in aprotic solvents, but for longer times. When using carboxylated active principles (for example ibuprofen, indomethacin, ofloxacine, rufloxacine) the reaction can be carried out after activation of the carboxylic group with known methods: use of CMPJ, transformation of the carboxyl into 4-nitrophenyl ester, N-hydroxysuccinimide ester, 1-hydroxy-benzotriazolyl ester, etc. In this case, it can be more convenient (mainly in terms of reproducibility of amount of bound active principle) to use the process a-c-b, namely binding the carboxylated active principle (after activation) to the polymer and then carrying out the cross-linking reaction.

The complexes with copper, zinc or iron ions are prepared by treating the cross-linked, "quenched" polymer with aqueous solutions (optionally with a suitable co-solvent) of inorganic salts of said elements, under conditions which depend on the nature of both the polymer and the ion. The metal ions content varies depending on the operative conditions, in particular on polymer to ion molar ratio, concentration, pH and cross-linking degree.

The cross-linked polymers obtainable according to the invention have advantageous properties in terms of chemical-physical characteristics, biocompatibility, tolerability and stability to chemical and metabolic hydrolysis, which make them suitable in various fields, in particular in the biomaterials field and, more generally, in the pharmaceutical and

biomedical fields.

Examples of said applications comprise the use thereof for the preparation of plasters or other transdermal forms, surgical or vascular prostheses, matrices with controlled-release of the active principles, coating films for wounds, cutaneous fillers, substitutes for biological fluids, biocompatible sponges, antiadhesive gels and, in general, medical-surgical devices.

The following examples illustrate the invention in greater detail.

Example 1: Derivatives of hyaluronic acid, 26% deacetylated, 100% cross-linked with aspartic acid

26% Deacetylated hyaluronic acid (2.0 g, about 3.80 mmoles), prepared according to Takehiko Wada et Al. (Industrial Biochnological Polymers- C.G. Gebelein & C.E. Carraher Editors- Technomic Publ.- 1995, pages 121-157) is dissolved in dry DMF, under stirring and nitrogen, and the solution is added with a large excess of aspartic acid p-nitrophenylester (Bachem Feinchemikalien AG). The reaction mixture is left under stirring for about 6 hours, then filtered through porous septum, concentrated under vacuum to about ¼ the starting volume and then added with distilled water in large excess. After standing at a temperature of about 4°C for 12 hours, the product is filtered under vacuum, dissolved in water and freeze-dried.

Example 2: Derivatives of hyaluronic acid 55% deacylated, with 50% of the free amino groups cross-linked with aspartic acid and then "quenched" by sulphation of the residual amino groups.

Deacylated hyaluronic acid is prepared according to Example 1. The dry solution of the product in DMF is added with an amount of aspartic acid nitrophenylester (Bachem Feinchemikalien AG) equivalent to a molar ratio of 1 (deacetylated HY) to X (desired cross-linking degree) in the same solvent. After standing, the solution is filtered, avoiding humidity, then

treated at 0°C with the pyridine/SO_3 complex. After suitable time, the solution is filtered, concentrated under vacuum to 1/10 the starting volume, then diluted with water and neutralized with sodium hydroxide. After clarifying filtration, the solution is freeze-dried.

CLAIMS

1. A process for the preparation of cross-linked polymers by reacting macromolecules containing primary or secondary amino groups with suitably activated dicarboxylic acids, which comprises:

a) activating the dicarboxylic acid carboxy groups in anhydrous aprotic solvent;

b) reacting the polyamino polymer, optionally previously subjected to partial "quenching" reaction of the amino groups;

c) optionally reacting the product from step b) with "quenching" agents of the residual amino groups.

2. A process as claimed in claim 1 wherein the amino groups "quenching" agents are selected from sulphation agents, succinic anhydride, acrylic acid N',N'-dialkylamides or alkyl esters, suitably activated carboxy derivatives having pharmacological activity.

3. A process as claimed in claim 1 or 2 wherein the macromolecules are selected from:

- hyaluronic acids (of bacterial or tissular origin) with different deacetylation degrees;
- collagens with different molecular weights;
- elastins with different hydrolysis degrees;
- chitosans with different molecular weights;
- polylysines with different polycondensation degrees with acetylated or anyway protected N-terminus;
- poly (vinylamines) of general formula:

$$[\ -CH_2-\underset{\displaystyle N-R'\\ \displaystyle R''}{CH}-\ ]\ n$$

R'= R"= H or R'= alkyl (linear or branched C_1-C_{12}) and R"= H;

- poly (acrylamines), or poly (allylamines), of general formula:

$$[\ -\underset{\displaystyle CH_2-NH_2}{CH}-CH_2-\ ]\ n$$

- poly(iminoethylene) [or poly(ethyleneimines)] of general formula:

$$[-\ NH-CH_2-CH_2]\ n;$$

- poly [4, (5)- vinyl-imidazoles] (P4VI);
- poly [aminoethylmethacrylates];
- poly [β-aminoethyl] vinyl ethers of general formula:

$$[\ -\ CH_2-\underset{\displaystyle O-CH_2-CH_2-NH_2}{CH}-\ ]n$$

4. A process as claimed in claim 1 wherein the dicarboxylic acids are selected from:

i) dicarboxylic acids of general formula:

$$HOOC-(X)n-\underset{\displaystyle Y}{COOH}$$

wherein:

n is an integer of 2 to 18;

X is an alkylene chain, linear or branched, saturated or unsaturated, comprising 1 to 10 carbon atoms, optionally containing nitrogen or oxygen heteroatoms, for example amino acidic residues;

Y is an alkylene chain, linear or branched, saturated or unsaturated, comprising 1 to 10 carbon atoms, preferably 1 to 6 atoms, optionally containing, also in the side chains, groups of formula: -NRR' (wherein: R

and R' = alkyl or acyl groups); -OR" (wherein: R"= H, alkyl or aryl and/or acyl groups); -COOR'" (wherein R'" = C_1-C_{10} alkyl groups, optionally branched or containing aromatic cycles or heterocycles);

ii) dicarboxylic amino acids, such as aspartic or glutamic acids, or the bi-condensed derivatives thereof, such as carboxy terminal monoesters;

iii) di- or poly-peptides deriving from the condensation of at least one acidic amino acid and neutral or basic amino acids;

iv) α- o β- malic acids or polymers thereof with low M.W.

5. A process as claimed in claim 1 wherein the dicarboxylic acid is activated by reacting the corresponding tetrabutylammonium salt with chloromethylpyridine iodide (CMPJ), in anhydrous solvents and under nitrogen.

6. Cross-linked polymers obtainable by the process of claims 1-5.

7. Complexes of the cross-linked polymers of claim 6 with metal cations.

8. The use of the cross-linked polymers or of the complexes of claims 6 or 7 for the preparation of pharmaceutical or dermocosmetic formulations, or of medical/surgical devices.

INTERNATIONAL SEARCH REPORT

In ational Application No
PCT/EP 01/05031

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C08B37/08 C08J3/24 C08K5/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C08B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	PATENT ABSTRACTS OF JAPAN vol. 12, no. 258 (C-513), 20 July 1988 (1988-07-20) & JP 63 044884 A (FUJI BOSEKI KK), 25 February 1988 (1988-02-25) abstract & DATABASE WPI Week 198814 Derwent Publications Ltd., London, GB; AN 1988-094812 abstract	1,3-5,8
X	PATENT ABSTRACTS OF JAPAN vol. 13, no. 171 (C-588), 24 April 1989 (1989-04-24) & JP 64 003116 A (NIPPON OIL & FATS CO LTD), 6 January 1989 (1989-01-06) abstract	1,3-5,8

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 August 2001	24/08/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Lensen, H

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Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

In ational Application No
PCT/EP 01/05031

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication.where appropriate, of the relevant passages	Relevant to claim No.
X	DE 44 39 575 A ("PERMSELECT"GESELLACHAFT FÜR ZELLSTRUKTURIERTE MATERIALIEN) 9 May 1996 (1996-05-09) column 1, line 48 - line 55	6,8

1

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

In ational Application No
PCT/EP 01/05031

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
JP 63044884 A	25-02-1988	JP 1621821 C JP 2036233 B	09-10-1991 16-08-1990
JP 64003116 A	06-01-1989	NONE	
DE 4439575 A	09-05-1996	NONE	